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L-Valyl-L-serine trihydrate

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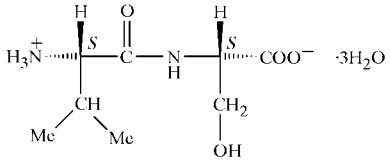
The valine side chains in the crystal structure of the title compound [systematic name: 2-(2-ammonio-3-methylbutanamido)-3-hydroxypropanoate trihydrate], $C_8H_{16}N_2O_4\cdot 3H_2O$, stack along an *a* axis of 4.77 Å to form hydrophobic columns surrounded by remarkable water/hydroxyl shells. The peptide main chains are connected by hydrogen bonds in two-dimensional layers. The peptide molecules in each layer are related only by translation, and generate a very rare pattern. This is rendered possible through the formation of the shortest C^{α}—H···O(carboxylate) interaction ever recorded.

Comment

As part of a systematic survey of dipeptides with one hydrophobic and one hydrophilic residue (Netland *et al.*, 2004), the structure of L-valyl-L-serine trihydrate, (I), has been determined.



(I)

The asymmetric unit of (I), with one peptide molecule and three water molecules, is shown in Fig. 1. The peptide main chain is quite extended, as reflected by the torsion angles given in Table 1. The valine side chain has a common *trans*/*gauche*− orientation for N1—C1—C2—C3/N1—C1—C2—C4, while a search in the Cambridge Structural Database (CSD, Version 5.25 of November 2003; Allen, 2002) shows that *gauche*+ for N2—C6—C7—O2 represents the most frequently observed serine conformation.

Fig. 2 illustrates the crystal packing pattern of (I). The peptide main chains generate layers, shown edge-on in Fig. 2, through hydrogen bonding. The most notable structural feature is the fact that the molecules in a layer are lined up perpendicular to the unique axis, rather than along it as one might expect. Consequently, all valine side chains point in the same direction. Under these circumstances, the hydrophobic groups cannot form separate layers, as they normally do in peptide crystals with a tight two-dimensional association of peptide main chains. Rather, the valine side chains are stacked into hydrophobic columns along the very short *a* axis (4.77 Å); we find fewer than 20 other peptides with a shorter crystallographic axis in the CSD. Each column is surrounded by a hydrophilic shell of water molecules and serine hydroxyl groups in a quite unusual manner. Numerous C—H···O contacts are involved, including C4—H42···O3($x+1, y, z+1$) (Fig. 2), with a H···O distance of 2.59 Å (Table 2); the rest of the contacts have H···O distances greater than 2.80 Å. The construction of a related water cage around a valine side chain was observed for L-phenylalanyl-L-valine (Görbitz, 2002), with comparable H···O and C···O distances.

Out of about 100 distinctly different dipeptide structures with a zwitterionic peptide main chain in the CSD, 37 contain hydrogen-bonded layers in which each amine group donates H atoms to carboxylate groups in two independent peptide molecules that are related by a simple unit-cell translation, or in some cases with $Z' > 1$ by pseudotranslational symmetry. Consecutive molecules in the resulting head-to-tail chains (Suresh & Vijayan, 1985) are usually related by a twofold screw operation in space group $P2_1$ or $P2_12_12_1$. In (I), the layers generated by hydrogen bonding between the peptide main chains involve molecules related purely by translation

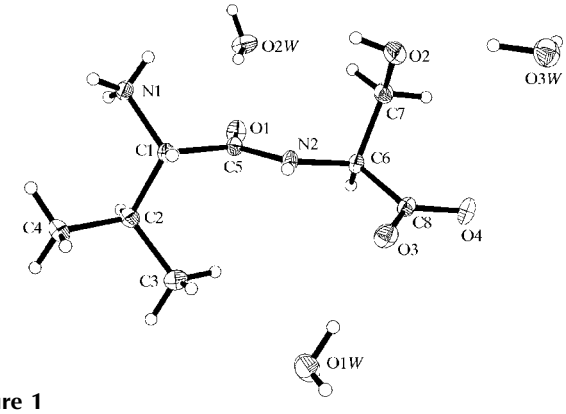


Figure 1
The molecular structure of (I). Displacement ellipsoids are shown at the 50% probability level and H atoms are shown as spheres of arbitrary size.

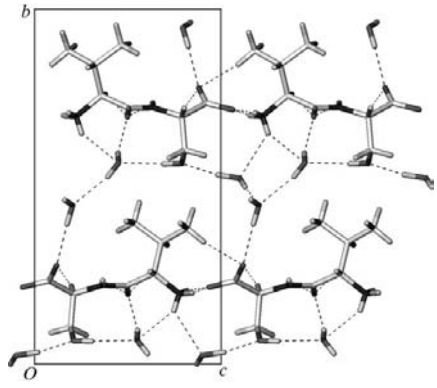


Figure 2
The molecular packing and unit cell of (I), viewed along the *a* axis. Hydrogen bonding is indicated by dashed lines.

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(Fig. 3), a phenomenon observed for just eight other dipeptide structures. Only the structure of L-glutamyl-L-aspartic acid hydrate, (II) (Eggleston & Hodgson, 1985), in space group $P1$, contains a fairly similar pattern (Fig. 3). The main differences between (I) and (II) concern a long N—H···O hydrogen bond in (II) (labelled 1 in Fig. 3; H···O = 2.50 Å and N—H···O = 143°) that has normal dimensions for this type of interaction in (I) (1.93 Å and 170°; Table 2), and a weak secondary interaction in (II) (labelled 2 in Fig. 3; 2.60 Å and 120°) that is missing in (I) (3.18 Å and 94°). A comparison of the main-chain conformations shows significant differences; the values for ψ_1, ω_1, φ_2 and ψ_T [N1—C1—C5—N2, C1—C5—N2—C6, C5—N2—C6—C8 and N2—C6—C8—O3 in (I)] are 148.0, 161.3, −118.2 and −31.9°, respectively, in (II), compared with 134.16 (7), 174.68 (7), −160.24 (8) and 0.38 (10)°, respectively, in (I) (Table 1).

The classic paper by Suresh & Vijayan (1985) on head-to-tail chains lists a series of theoretical layered aggregation patterns for dipeptides, but does not include the pattern illustrated in Fig. 3. The reason is probably that, at the time, the importance of C—H···O interactions had not yet been realised. As is evident from Fig. 3, C^{α}—H···O(carboxylate) interactions play a key role in completing the hydrogen-bond network of (I). Thus, the tapes with carbonyl acceptors, familiar from about 12 other dipeptide structures, have C_1^{α}—H as well as >N—H donors. More uncommon is the C_2^{α}—H···O(carboxylate) interaction (labelled 3 in Fig. 3). A total of about 250 peptide structures in the CSD have an unprotected negatively charged C-terminal carboxylate group. Within this subset, there are 33 C^{α}—H···O(carboxylate) interactions (in 25 structures) with H···O distance < 2.60 Å, but only eight (in six structures) with H···O < 2.40 Å. In (I), H61···O3($x+1, y, z$) is 2.28 Å, the smallest value recorded for this type of contact; the corresponding distance in (II) is 2.51 Å.

Apart from the presence of two amino–carboxylate hydrogen bonds, there are few similarities between the structure of (I) and the structures of L-alanyl-L-serine (Jones *et al.*, 1978) and the retroanalogue L-seryl-L-valine, studied previously as part of our ongoing investigation (Moen *et al.*, 2004). This is not unexpected, since (I) was crystallized as a trihydrate, while the other two structures are devoid of solvent water moleules.

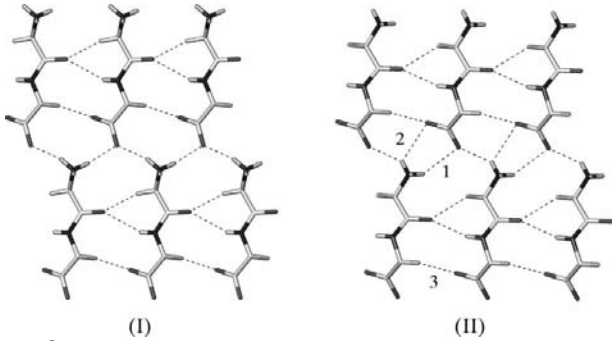

Figure 3
The hydrogen bonding between the peptide main chains in the structures of (I) and (II). See *Comment* for a discussion of the 1, 2 and 3 labelling.

Experimental

The title compound was obtained from Bachem. Crystals were grown by diffusion of acetonitrile into 30 µl of an aqueous solution containing about 1 mg of the peptide.

Crystal data

$C_8H_{16}N_2O_4\cdot 3H_2O$
$M_r = 258.28$
Monoclinic, $P2_1$
$a = 4.7695$ (2) Å
$b = 16.1323$ (5) Å
$c = 8.6789$ (3) Å
$\beta = 103.6360$ (10)°
$V = 648.96$ (4) Å^3
$Z = 2$
$D_x = 1.322$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 6036 reflections
$\theta = 2.4$–37.8°
$\mu = 0.12$ mm^{-1}
$T = 105$ (2) K
Needle, colourless
0.90 × 0.30 × 0.05 mm

Data collection

Siemens SMART CCD area-detector diffractometer
Sets of exposures each taken over 0.3° ω rotation scans
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1996)
$T_{min} = 0.738$, $T_{max} = 0.994$
9845 measured reflections
3564 independent reflections
3309 reflections with $I > 2\sigma(I)$
$R_{int} = 0.026$
$\theta_{max} = 37.8$°
$h = -8 \rightarrow 8$
$k = -23 \rightarrow 27$
$l = -14 \rightarrow 14$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.031$
$wR(F^2) = 0.083$
$S = 1.07$
3564 reflections
189 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0542P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.38$ e Å^{-3}
$\Delta\rho_{min} = -0.23$ e Å^{-3}

Table 1
Selected torsion angles (°).

N1—C1—C5—N2	134.16 (7)	N1—C1—C2—C3	171.31 (9)
C1—C5—N2—C6	174.68 (7)	N1—C1—C2—C4	−65.36 (9)
C5—N2—C6—C8	−160.24 (8)	N2—C6—C7—O2	60.42 (9)
N2—C6—C8—O3	0.38 (10)	C6—C7—O2—H5	−79.3 (16)

Table 2
Hydrogen-bond geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1···O2W^{i}	0.80 (2)	2.53 (2)	3.1472 (12)	134 (2)
N1—H1···O3W^{ii}	0.80 (2)	2.52 (2)	3.0816 (12)	128 (1)
N1—H2···O4^{iii}	0.88 (2)	1.89 (2)	2.7413 (10)	163 (2)
N1—H3···O4^{ii}	0.85 (2)	1.93 (2)	2.7752 (9)	170 (2)
N2—H4···O1^{i}	0.79 (2)	2.48 (2)	3.1233 (9)	140 (2)
O2—H5···O2W^{i}	0.82 (2)	2.07 (2)	2.8917 (12)	174 (2)
C1—H11···O1^{i}	1.00	2.41	3.2783 (10)	146
C4—H42···O3^{ii}	0.98	2.59	3.4086 (12)	140
C6—H61···O3^{iv}	1.00	2.28	3.2645 (11)	169
O1W—H11W···O3^{v}	0.88 (2)	1.97 (2)	2.8423 (11)	177 (2)
O1W—H12W···O3W^{vi}	0.80 (2)	2.02 (2)	2.7997 (12)	165 (2)
O2W—H21W···O1^{v}	0.76 (2)	2.08 (3)	2.7915 (11)	157 (2)
O2W—H22W···O1W^{vii}	0.81 (3)	2.07 (2)	2.8490 (11)	161 (2)
O3W—H31W···O1W^{viii}	0.79 (2)	2.06 (2)	2.8492 (13)	174 (2)
O3W—H32W···O2^{v}	0.99 (2)	1.95 (2)	2.8849 (11)	157 (2)

Symmetry codes: (i) $x-1, y, z$; (ii) $x+1, y, z+1$; (iii) $x, y, z+1$; (iv) $x+1, y, z$; (v) x, y, z; (vi) $-x-1, y+\frac{1}{2}, -z$; (vii) $-x+1, y-\frac{1}{2}, -z+1$; (viii) $-x, y-\frac{1}{2}, -z$.

Positional parameters were refined for H atoms bonded to N and O atoms. Other H atoms were positioned with idealized geometry and fixed C—H distances in the range 0.98–1.00 Å. U_{iso}(H) values were $1.2U_{eq}$ of the carrier atom, or $1.5U_{eq}$ for amino and methyl

groups and for water molecules. In the absence of significant anomalous scattering effects, 1916 Friedel pairs were merged. The absolute configuration was known for the purchased material.

Data collection: *SMART* (Bruker, 1998); cell refinement: *SAINT* (Bruker, 2001); data reduction: *SAINT*; program(s) used to solve structure: *SHELXTL* (Bruker, 2000); program(s) used to refine structure: *SHELXTL*; molecular graphics: *SHELXTL*; software used to prepare material for publication: *SHELXTL*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SX1167). Services for accessing these data are described at the back of the journal.

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